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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/461,090	ULLRICH ET AL.	
	Examiner	Art Unit	
	FRANK W. LU	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 December 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Appeal Brief

1. In view of the appeal brief filed on June 27, 2008, **PROSECUTION IS HEREBY REOPENED**. New rejections are set forth below. The claims pending in this application are claims 40-45, 47, and 48. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

To avoid abandonment of the application, applicant must exercise one of the following two options:

file a replay under 37 CFR 1.111; or

request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1,131, or 1.132) or other evidence are permitted. See 37 CFR 1.93 (b) (2).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. New Matter

Claims 40-45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First, independent claims 45 and 47 have a limitation "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor". Although page 2, lines 5-22 of the specification describes that the activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, the specification fails to define or provide any disclosure to support such claim limitation. Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2, lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only support that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, although the examiner agrees that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not limit to "growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification, the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" recited in claims 45 and 47 is a new matter. Second, independent claim 45 has a limitation "a compound which acts on a growth factor precursor" while independent claim 47 has a limitation "a compound which directly binds to a growth factor precursor". Although original filed claim 6 describes that the modulator acts on a G-protein, a G-protein coupled receptor and/or a proteinase such as batimastat which can bind to

metalloprotease and block EGF release from EGF precursor (see page 9, second paragraph) and page 3, line 15 of the specification suggested by appellant describes CRM197, a catalytically inactive form of the diphtheria toxin, which specifically binds to proHB-EGF and which is capable of blocking the processing of proHB-EGF by metalloproteinase, the specification does not describe any other compound which acts on a growth factor precursor as recited in claim 45 and any other compound which directly binds to a growth factor precursor as recited in claim 47. Third, although page 3, line 15 of the specification suggested by appellant describes CRM197, a catalytically inactive form of the diphtheria toxin, which specifically binds to proHB-EGF and which is capable of blocking the processing of proHB-EGF by metalloproteinase, since claim 47 does not require that a compound which directly acts on a growth factor precursor is CRM197 and a compound which directly acts on a growth factor precursor can be other compound which is not CRM197, the phrase "a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claim 47 is a new matter. Fourth, although the specification describes "the present invention provides methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma. More particular, the growth of human prostate cancer cells may be inhibited by treatment with proteinase inhibitors such as batimastat" (see page 3, third paragraph), the specification does not support to *in vitro* methods recited in claims 44 and 45 wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells. Furthermore, since methods

for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma mentioned in page 3, third paragraph of the specification and the method for identifying a test compound for modulating G-protein mediated signal transduction recited in claim 44 and the method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction recited in claim 45 are different methods which have different method steps and different purposes, appellant's statement "treating the tumors discussed on page 3 of the present application using the present invention inherently results in the treatment of a cancer cell as in claim 45" is incorrect. In addition, although page 4, lines 2-4 of the specification describes that "the contacting step may occur in vitro, e.g. in a cell culture or *in vivo,* e.g. in a subject in need of medical treatment", the cell culture described by page 4, lines 2-4 of the specification is not limited to cancer cell culture. Therefore, the phrase "wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cell" recited in claims 44 and 45 is a new matter.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Response to Arguments

I. In page 5, last paragraph bridging to page 8, first paragraph of the Brief on Appeal, appellant argues that: (1) in view of page 2, lines 5-22, page 10, lines 25-32, page 11, lines 26-32, and page 12, lines 1-13 of the specification, and original filed claims 1 and 3, the language "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not new matter; and (2) "the exact language used in the claims does not need to appear in the specification".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although page 2, lines 5-22 of the specification describes that the activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, the specification fails to define or provide any disclosure to support "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor". Although original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2, lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction. Furthermore, page 10, lines 25-32, page 11, lines 26-32, and page 12, lines 1-13 of the specification suggested by appellant are examples for EGF-EGFR systems and are not any of growth-factor receptor in the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor". In addition, although the examiner agrees

that the exact language used in the claims does not need to appear in the specification, since the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not limit to "growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction" and is much broader than the disclosure in the specification, the phrase "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" recited in claims 45 and 47 is a new matter.

II. In page 9, last paragraph bridging to page 10, first paragraph of the Brief on Appeal, appellant argues that "[A]pplicants point out the disclosure on page 3, lines 23-27 of the present application which states that 'the present invention provides methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma'. In addition, pages 16 and 17 in the present application discuss human prostate cancer cells and page 6, lines 5-14 discuss the claimed method for identifying modulators of G-protein mediated signal transduction using a cell which contains a growth factor receptor. Since page 3 of the present application indicates that the present invention can be used to treat pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumors, one skilled in the art would know that cells from these tumors have a growth factor receptor tyrosine kinase and thus one would reasonably expect such cells to be useful to identify test compounds as in claim 44. Regarding claim 45, applicants point out that treating the tumors discussed on page 3 of the present application using the present invention inherently results in the treatment of a cancer cell as in claim 45. In addition, page 4, lines 2-4 indicate that the contacting step may occur in vitro, e.g. in a cell culture or *in vivo,* e.g. in a

subject in need of medical treatment. Therefore, the present inventors were in possession of and disclosed the subject matter claimed in claims 44 and 45".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although the specification describes "the present invention provides methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma. More particular, the growth of human prostate cancer cells may be inhibited by treatment with proteinase inhibitors such as batimastat" (see page 3, third paragraph), the specification does not support to *in vitro* methods recited in claims 44 and 45 wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells. Furthermore, since methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma mentioned in page 3, third paragraph of the specification and the method for identifying a test compound for modulating G-protein mediated signal transduction recited in claim 44 and the method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction recited in claim 45 are different methods which have different method steps and different purposes, appellant's statement "treating the tumors discussed on page 3 of the present application using the present invention inherently results in the treatment of a cancer cell as in claim 45" is incorrect. In addition, although page 4, lines 2-4 of the specification describes that "the contacting step may

occur in vitro, e.g. in a cell culture or *in vivo,* e.g. in a subject in need of medical treatment", the cell culture described in page 4, lines 2-4 of the specification is not limited to cancer cell culture. Therefore, the phrase "wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cell" recited in claims 44 and 45 is a new matter.

4. Scope of Enablement

Claims 40-45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for blocking EGF receptor transactivation by G-protein-coupled receptors in *in vitro* by inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, does not reasonably provide enablement for: (1) identifying a test compound for modulating G-protein mediated signal transduction in *in vivo* by contacting a cancer cell containing any kind of receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of any kind of ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 44; (2) modulating growth factor receptor activation in *in vivo* by modulating a G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and

wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates any kind of growth factor receptor, wherein one or more tyrosine residues of any kind of growth factor receptor are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 45; and (3) modulating growth factor receptor activation in *in vivo* by modulating G-protein mediated signal transduction comprising stimulating G protein mediated signal transduction in a cell having any kind of growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates any kind of growth factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor recited in claims 40-43, 47, and 48. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of The Invention

The claims are drawn to a method for identifying a test compound for modulating G-protein mediated signal transduction and a method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claim 44 encompasses a method for identifying a test compound for modulating G-protein mediated signal transduction in *in vivo* by contacting a cancer cell containing any kind of receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of any kind of ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor

cells. Claim 45 encompasses a method for modulating growth factor receptor activation in *in vivo* by modulating a G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates any kind of growth factor receptor, wherein one or more tyrosine residues of any kind of growth factor receptor are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells. Claim 47 encompasses a method for modulating growth factor receptor activation in *in vivo* by modulating G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cell having any kind of growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates any kind of growth factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor.

Working Examples

The specification provides working examples (see pages 9-17) to show that inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, blocks EGF receptor transactivation by G-protein-coupled receptors in *in vitro*. The specification provides no working example related to the claimed inventions recited in claims 40-45, 47, and 48. For example, besides EGFR, the specification provides no working example to show that metalloproteinase is correlated with the transactivation of any other receptor tyrosine kinase by G-protein-coupled receptor.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification teaches that inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, blocks EGF receptor transactivation by G-protein-coupled receptors in *in vitro* (see pages 9-17), the specification does not provide a guidance for: (1) identifying a test compound for modulating G-protein mediated signal transduction in *in vivo* by contacting a cancer cell containing any kind of receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of any kind of ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 44; (2) modulating growth factor

receptor activation in *in vivo* by modulating a G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates any kind of growth factor receptor, wherein one or more tyrosine residues of any kind of growth factor receptor are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 45; and (3) modulating growth factor receptor activation in *in vivo* by modulating G-protein mediated signal transduction comprising stimulating G protein mediated signal transduction in a cell having any kind of growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates any kind of growth factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor recited in claims 40-43, 47, and 48. Furthermore, there is no experimental condition and/or

experimental data in the specification to support the claimed invention. Although it is known in the art that inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, blocks EGF receptor transactivation by G-protein-coupled receptors in *in vitro* (see Prenzel et al., Nature, 402, 884-888, 1999), during the process of the prior art search, the examiner has not found any prior art which is related to the claimed method recited in claims 40-45, 47, an 48.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether: (1) a test compound for modulating G-protein mediated signal transduction can be identified in *in vivo* by contacting a cancer cell containing any kind of receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of any kind of ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 44; (2) any kind of growth factor receptor activation can be modulated in *in vivo* by modulating a G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members

of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates any kind of growth factor receptor, wherein one or more tyrosine residues of any kind of growth factor receptor are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 45; and (3) any kind of growth factor receptor activation can be modulated in *in vivo* by modulating G-protein mediated signal transduction comprising stimulating G protein mediated signal transduction in a cell having any kind of growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates any kind of growth factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor recited in claims 40-43, 47, and 48.

First, since the claims do not require that the methods recited in 40-45, 47, and 48 are performed in *in vitro*, the methods recited in 40-45, 47, and 48 can be read as an *in vivo* method. Since it is known that there are a number of differences between *in vitro* models and the *in vivo* situation (see White et al., Pharmacotherapy, 21, 292S-301S, 2001), it is unclear how to perform the methods recited in 40-45, 47, and 48 in *in vivo* based on *in vitro* methods in the specification.

Second, it is known in the art that receptor tyrosine kinases (RTKs) are the high affinity cell surface receptors for many polypeptide growth factors, cytokines and hormones and includes RTK class I (EGF receptor family), RTK class II (Insulin receptor family), RTK class III (PDGF receptor family), RTK class IV (FGF receptor family), RTK class V (VEGF receptors family), RTK class VI (HGF receptor family), RTK class VII (Trk receptor family), RTK class IX (AXL receptor family), RTK class X (LTK receptor family), RTK class XI (TIE receptor family), RTK class XII (ROR receptor family), RTK class XIII (DDR receptor family), RTK class XV (KLG receptor family), RTK class XVI (RYK receptor family) and RTK class XVII (MuSK receptor family) and EGF receptor family is class I of receptor tyrosine kinases (see the definition for receptor tyrosine kinases from Wikipedia, the free encyclopedia) and includes ErbB-1 (EGFR), ErbB-2 (HER2), ErbB-3 (HER3), and ErbB-4 (HER4) (see the definition for ErbB from Wikipedia, the free encyclopedia). Although the specification shows that inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, blocks EGF receptor transactivation by G-protein-coupled receptors (GPCRs) in *in vitro* (see pages 9-17) and transactivation by GPCRs has also been shown for other RTKs, such as the platelet-derived growth factor receptor (PDGFR) (see Table 2 and page 652 from Wezker et al., Nature Reviews Molecular Cell Biology, 4, 651-657, 2003), there is no evidence to show that transactivation of other RTKs by G-protein-coupled receptors (GPCRs) has involvement of metalloproteinases. For example, although new, latent ligands of PDGFR-PDGFC and PDGFD have recently been discovered, their possible participation in a transactivation mechanism has not yet been investigated. There is also little known about the detailed mechanisms for the GPCR transactivation of other RTKs, such as the insulin growth factor-1 (IGF-1) receptor, the neurotrophin receptors TrkA and TrkB,

and the fibroblast growth factor (FGF) receptor (see Table 2 and page 652 from Wezker et al., Nature Reviews Molecular Cell Biology, 4, 651-657, 2003). Since additional pathways of EGFR transactivation that do not involve metalloproteinase-mediated HB-EGF release have also been identified (see right column in page 651 and left column in page 652, from Wezker et al., Nature Reviews Molecular Cell Biology, 4, 651-657, 2003), it is possible that transactivation of other RTKs by G-protein-coupled receptors (GPCRs) may not involve metalloproteinases. Thus, in view of the specification, it is unclear how any kind of receptor tyrosine kinase can be activated by G-protein mediated signal transduction such that a test compound for modulating G-protein mediated signal transduction can be identified as recited in claim 44, how other members of the EGFR family such as ErbB-2 or ErbB-3 or ErbB-4 can be modulated by modulating a G-protein mediated signal transduction as recited in claim 45, and how any kind of growth factor receptor tyrosine kinase can be modulated by modulating a G-protein mediated signal transduction as recited in claims 47 and 48.

Third, since it is known that growth hormone can induce tyrosine phosphorylation of epidermal growth factor receptor (EGFR), one of receptor tyrosine kinases, by kinase Jak2 (see abstract from Yamauchi et al., Nature, 390, 91-96, 1997, a paper from Evidence Appendix in the Brief on Appeal), phorbol ester phorbol 12-myristate 13-acetate (PMA) induced tyrosine phosphorylation of the ErbB receptors (EGFR is ErbB-1) is dependent on protein kinase C (see page 311172 from Emkey et al., J. Biol. Chem., 272, 31172-31181, 1997, a paper from Evidence Appendix in the Brief on Appeal), and claim 44 does not require that the test compound must act on a precursor of a ligand of the receptor tyrosine kinase and the test compound is not either growth hormone or PMA, it is unclear, when receptor tyrosine kinase such as EGFR is activated

by tyrosine phosphorylation upon exposure of the cancer cell to said test compound, why the receptor tyrosine kinase such as EGFR is not activated based on kinase Jak2 when the test compound is growth hormone or based on protein kinase C when the test compound is PMA but the receptor tyrosine kinase such as EGFR must be activated by G-protein mediated signal transduction such that a test compound for modulating G-protein mediated signal transduction can be identified as recited in claim 44.

Fourth, since claims 45 and 47 do not require that a compound which acts on growth factor precursor is a specific compound and it is known that CRM197 only inhibit HB-EGF and proHB-EGF specifically but not other EGF receptor ligand (see page 1238, left column from Nishida et al., Arterioscler. Thromb. Vasc Biol., 20, 1236-1243, 2000), when a compound is CRM197 and growth factor precursor is not proHB-EGF, it is unclear how the growth factor precursor can be cleaved and G protein mediated extracellular signal transduction pathway can be modulated.

In view of above discussions, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether (1) a test compound for modulating G-protein mediated signal transduction can be identified in *in vivo* by contacting a cancer cell containing any kind of receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of any kind of ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated

signal transduction wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 44; (2) any kind of growth factor receptor activation can be modulated in *in vivo* by modulating a G-protein mediated signal transduction by stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates any kind of growth factor receptor, wherein one or more tyrosine residues of any kind of growth factor receptor are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells as recited in claim 45; and (3) any kind of growth factor receptor activation can be modulated in *in vivo* by modulating G-protein mediated signal transduction comprising stimulating G protein mediated signal transduction in a cell having any kind of growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates any kind of growth

factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor recited in claims 40-43, 47, and 48.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples related to the claimed inventions recited in claims 40-45, 47, and 48 and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 40-45, 47, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 44 is rejected as vague and indefinite. Although claim 44 is directed to a method for identifying a test compound for modulating a G-protein mediated signal transduction, from the method steps in the claim, it is unclear that, in which situation, the test compound can be

considered as a compound that has an ability to modulate a G-protein mediated signal transduction. Please clarify.

Response to Arguments

In page 10, last paragraph bridging to page 11, first paragraph of the Brief on Appeal, appellant argues that "[C]laim 44 includes the step of 'evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction'. One skilled in the art would know that if G-protein mediated receptor tyrosine kinase activation does not occur upon the exposure of the cancer cell to a test compound, then the test compound has modulated the G-protein mediated signal transduction. Claim 44 recites that the test compound is suspected to act on a precursor of a ligand of the receptor tyrosine kinase. If the test compound binds or acts on a precursor of a ligand of the receptor tyrosine kinase the G-protein mediated signal transduction pathway will be interrupted and there will not be G-protein mediated receptor tyrosine kinase activation. Applicants contend that one skilled in the art would know that if the test compound binds or acts on a precursor of a ligand of the receptor tyrosine kinase, there will be no G-protein mediated receptor tyrosine kinase activation. In view of the above discussion, applicants contend that claim 44 is not vague or indefinite".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although claim 44 requires "evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction thereby

identifying a test compound for modulating G-protein mediated signal transduction", this phrase does not indicates that, in which situation, the test compound can be considered as a compound that has an ability to modulate a G-protein mediated signal transduction. Furthermore, the phrase "evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction" does not make sense because it is unclear, in view of the claim, how "[O]ne skilled in the art would know that if G-protein mediated receptor tyrosine kinase activation does not occur upon the exposure of the cancer cell to a test compound, then the test compound has modulated the G-protein mediated signal transduction" and "one skilled in the art would know that if the test compound binds or acts on a precursor of a ligand of the receptor tyrosine kinase, there will be no G-protein mediated receptor tyrosine kinase activation".

8. Claim 45 or 47 is rejected as vague and indefinite. Although claim 45 or 47 is directed to a method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction, from the method steps in the claim, it is unclear why the receptor tyrosine kinase activation can be modulated by G-protein mediated signal transduction since modulating the growth factor receptor tyrosine kinase activation by G-protein-mediated signal transduction can not be completed by contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor as recited in claim 45 or contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor as recited in claim 47. Please clarify.

Response to Arguments

In page 11, last paragraph bridging to page 12, first paragraph of the Brief on Appeal, appellant argues that "[S]ince both claim 45 and claim 47 recite that the cell is contacted with a compound which directly binds to or acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor, applicants contend that one skilled in the art would know how the receptor tyrosine kinase activation is modulated by G-protein mediated signal transduction".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since modulating the growth factor receptor tyrosine kinase activation by G-protein-mediated signal transduction can not be completed by contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor as recited in claim 45 or contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor as recited in claim 47, it is unclear why the receptor tyrosine kinase activation can be modulated by G-protein mediated signal transduction.

9. Claim 45 is rejected as vague and indefinite because one or more tyrosine residue of what are phosphorylated based on the activation of said G-protein mediated signal transduction pathway. Please clarify.

Conclusion

10. No claim is allowed.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Frank W Lu /
Primary Examiner, Art Unit 1634
September 24, 2008